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10/591,658	08/15/2007	Makoto Yuasa	295973US0PCT	3124

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EXAMINER	
FIERRO, ALICIA	
ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
11/27/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/591,658	YUASA ET AL.	
	Examiner	Art Unit	
	Alicia L. Fierro	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-37* is/are pending in the application.

4a) Of the above claim(s) *33-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-32,36 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/24/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 20-37 are now pending in the instant application, according to the amended Listing of the Claims filed August 24, 2009. Original claims 1-19 have been cancelled.

Elections/Restrictions

2. Claims 33-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. In accordance with MPEP 818.01, "Election becomes fixed when the claims in an application have received an action on their merits by the office." MPEP 818.02(a) states that "The claims originally presented and acted upon by the Office on their merits determine the invention elected by an applicant in the application, and in any request for continued examination (RCE) which has been filed for the application. Subsequently presented claims to an invention other than acted upon should be treated as provided in MPEP 821.03."

3. Newly submitted claims 33-35 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The originally claimed invention and claims 33-35 are related as product and process of use. The inventions are distinct because the original invention, as claimed, can be used for another materially different process of using other than the processes as claimed. For example, the product can be used for *in vitro* toxicology or stability studies or for *in vitro* determination of the efficacy of oxygen scavenging.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 33-35 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Response to Arguments and Amendments

4. Applicants amendments filed August 24, 2009 have been entered. The amendments render moot the original rejection under 35 U.S.C. 103(a) and necessitated the new grounds of rejection applied below. Applicants argue that the rejections under 35 U.S.C. 112, first and second paragraphs are now moot because the new claims incorporate limitations from claims 5 and 6 which were not rejected in the first Office action. However, original claims 5 and 6 were in improper form and as stated in the first Office action at Page 5 were not further treated on the merits due to improper multiple dependencies. Now that the improper multiple dependency issue has been corrected, the rejections under 35 U.S.C. 112, first and second paragraphs now apply to the new claims as discussed below.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on August 24, 2009 was in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. Accordingly, these IDS documents were considered and signed copies of form 1449 have been enclosed herewith.

New Claim Rejections – 35 USC §112

(Second Paragraph)

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 20-32, 36 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Regarding claims 20 and 29 and dependent claims 24, 26, 28 and 30, it is unclear what is meant by the term "niosome-forming substance." No definition is given in the specification other than saying that "many compounds reported to produce a niosome can be used" (p. 6, lines 7-8). There is no indication of where such reports could be found, what properties are required to be present in order for a substance to be considered a niosome-forming substance. Since it is commonly known in the art that nonionic surfactants, with or without cholesterol, can be used to produce niosomes, the term will be interpreted as such for the purposes of applying art.

b. Regarding claims 20 and 29, an all claims dependent thereon, the claims recite formulae (I), (II) and (III) which contain the variable "M," for which no definition is provided. All variables of a chemical formula must be defined the first time they appear in the claims. Appropriate correction is required.

c. Claims 24-28 recites the limitation "the metal (M) is iron (Fe), manganese (Mn), cobalt (Co), copper (Cu), molybdenum (Mo), chromium (Cr), or iridium (Ir). There is

insufficient antecedent basis for this limitation in the independent claim 20, since the base claim does not provide and possible definition for the variable M.

d. Claim 29 refers to formulae (I), (II) and (III) which are structures and must be included in the claims. *Ex parte Fressola*, 27 USPQ 2d 1608: Claims must stand alone to define the invention and incorporation into claims by express references to the specification is not permitted. Although claim 20 shows the formulae, claim 29 is independent and must therefore stand alone to define the invention. Appropriate correction is required. Please import the appropriate structures into claim 29.

e. Claims 28-31 recite the following limitation:

> R_{27} and R_{28} indicate N-alkylammonio groups and one or more of metal [5,10,15,20-tetrakis(2-methylpyridyl)porphyrin] (MT2MPyP), metal[5,10,15,20-tetrakis(4-methylpyridyl)porphyrin] (MT4MPyP), or metal [[1,3,5,8-tetramethyl-2,4-divinyl-6,7-di(4-methylpyridylamideethyl)]porphyrin] (MPPIX-DMPyAm), wherein the metal (M) is iron (Fe), manganese (Mn), cobalt (Co), copper (Cu), molybdenum (Mo), chromium (Cr), or iridium (Ir).

This phrasing is indefinite for several reasons. Firstly, there is insufficient antecedent basis for R27 and R28 being anything other than N-alkylammonio groups as recited in base claim 20. Secondly, it is unclear how R27 and R28 could be *both* N-alkylammonio *and* one or more of the metalloporphyrin formulas recited. A variable can only be one functional group, and if several options are presented they should be separated by the word "or." Appropriate correction is required.

New Claim Rejections - 35 USC § 112

(First Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 20, 24, 26, and 28-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite the limitation that a "niosome-forming substance" is present in the claimed niosome. Applicant has not described the claimed genus in a manner that would indicate they were in possession of the full scope of the genus, or even to describe what the genus is comprised of.

Regarding the requirement for adequate written description of chemical entities, Applicant's attention is directed to the MPEP §2163. In particular, Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089, 118 S. Ct. 1548 (1998), holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plain for obtaining the claimed chemical invention." Eli Lilly, 119 F.3d at 1566. The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications under the 35 U.S.C. 112.1 "Written Description"

Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter aria*, "functional characteristics when coupled with a known or disclosed correlation between function and structure..." Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 316, 1324-25 (Fed. Cir. 2002) (quoting Guidelines, 66 Fed. Reg. at 1106 (emphasis added)). Moreover, although Eli Lilly and Enzo were decided within the factual context of DNA sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. Univ. of Rochester v. G.D. Searle & Co., 249 Supp. 2d 216, 225 (W.D.N.Y. 2003).

In the instant case, the claims are drawn to a metalloporphyrin-embedding niosome comprising a cationized metalloporphyrin complex of formula (I), (II) or (III) and a niosome-forming substance. The claimed "niosome-forming substance" encompass any substance capable of forming a noisome, both known and unknown. With regards to a definition of the niosome-forming substance, Applicants describe only that "many compounds reported to produce a niosome can be used" (p. 6, lines 7-8 of specification), and further give the example of nonionic surfactants or a mixture of nonionic surfactant and cholesterol or triacylglycerol. However, the examples described are only put forth as preferences and thus do not limit the definition of the claimed "niosome-forming substance." Based on Applicant's lack of description of this term other than non-limiting examples, it is not evident what other substances would be encompassed by this term/claim other than a nonionic surfactant or what functional limitations are required for a given substance to be considered a noisome-forming substance that would read on the instant claims. Applicants describe no "niosome-forming substances" other those

specifically disclosed as examples. Further there is no disclosure of a method for using *any* niosome-forming substance other than nonionic surfactants. Thus, no niosome-forming substances, other than those described by providing examples on page 6, are described adequately enough to allow one skilled in the art to ascertain that Applicant is in possession of the entire scope of the claimed genus or to immediately envisage all niosome-forming substances contemplated for use. As such, the claims lack adequate written description for the myriad of possible substances which could be considered niosome-forming substances.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

New Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the

claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

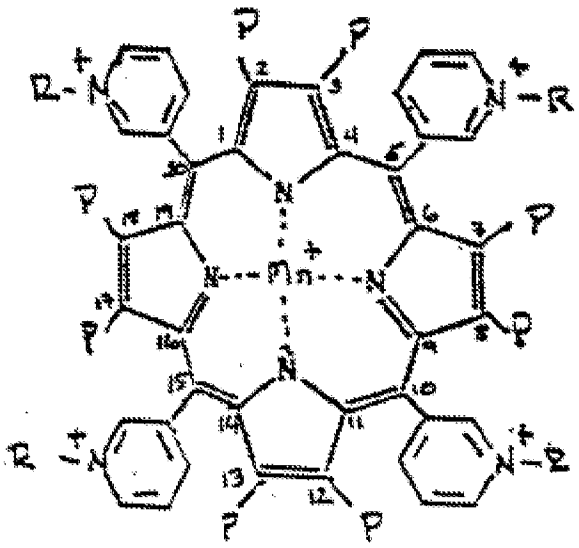
1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 20-32, 36 and 37 are rejected under 35 U.S.C. 103(a) as obvious over Nishihara et al. (US 2002/0164379), publication date November 7, 2002, in view of Fridovich et al. (WO 99/023097) and Baroli et al. *International Journal of Pharmaceutics,* 183 (1999).

12. Nishihara et al. teaches cationic metalloporphyrin complexes (see, for example, the complex of formula (4) on page 6) embedded in liposomes useful as ophthalmic compositions for the treatment of ocular diseases (see Abstract). The liposomes used can be lipid endoplasmic reticulum, and particular examples are given such as phosphatidyl choline, phosphatidyl serine, and others ([0071]). Nishihara et al. also teaches that additional components, such as cholesterol can be added, which is "useful in the formation of endoplasmic reticulum, the stabilization of

membrane, and the adjustment of permeability of liposome membrane" ([0072]). Nishihara et al. also describes the porphyrin complex as being preferable for its ability to act as an oxygen carrier. The differences between Nishihara et al. and the instant claims is that Nishihara does not teach the specific metalloporphyrin complexes of formula (I), (II) or (III) or a niosome-forming substance.

13. Fridovich et al. teach cationized metalloporphyrin complexes identical to those of the instant claims as mimetics of scavengers of reactive oxygen species having superoxide dismutase activity, describing complexes of Formula II as "preferred" (see p. 7).



Formula II

14. Fridovich teaches that the mimetics disclosed in the reference can be used "to protect against damage to the eye due to sunlight…as well as glaucoma and macular degeneration in the eye. The mimetics can also be used to protect against and/or treat cataracts" (p. 13, lines 9-15). The instant complexes manganese [5,10,15,20-tetrakis (2-methylpyridyl) porphyrin] and manganese [5,10,15,20-tetrakis (4-methylpyridyl) porphyrin] are disclosed several times

throughout the reference. For example, Example VII discloses the "ortho, meta, and para isomers of manganese(III) 5,10,15,20-tetrakis(N-methylpyridyl)porphyrin," where the ortho and para compounds are identical to the two instant compounds listed above, which reads on the disclosed generic formula (I) where R1-R4 are N-lower-alkylpyridyl (specifically N-methylpyridyl). Example V compares *in vitro* superoxide dismutase activity of the ortho and para complexes of Example VII. It discloses that the ortho compound has decreased toxicity due to its decreased ability to interact with and cleave DNA. In Example VII, it is disclosed that the ortho isomer has a weak interaction with DNA, which would make this particular complex desirable for *in vivo* use because it would not be expected to cause oxidative damage to DNA after administration.

15. Fridovich et al. does not disclose the cationized metalloporphyrin complexes or compositions embedded in liposomes. However, the complexes of Fridovich et al., which are identical to those of the instant claims, are disclosed for the same utility as the metalloporphyrin complexes of Nishihara et al. It would have been obvious at the time the invention was made for a person of ordinary skill in the art to embed the preferred complexes taught by Fridovich et al. in the liposomes taught by Nishihara et al. because the complexes are taught for the same purpose (i.e. oxygen scavenging and treatment of various ophthalmic disorders), and the complexes of Fridovich et al. solve the art-recognized problem of interaction and cleavage of DNA. Therefore, the complexes taught by Fridovich et al. would be reasonably expected to have a reduced toxicity while being useful for the same purpose as those of Nishihara et al.

16. Taken together, the Nishihara et al. and Fridovich et al. references do not teach embedding the cationized metalloporphyrin complexes of the instant claims in a niosome with a niosome-forming substance.

17. Baroli et al. discusses generally the utility of niosomes. They disclose that although liposomes tend to be the most used vesicular carrier systems, non-ionic surfactant vesicles (or niosomes) are being extensively studied due to their useful properties. Niosomes "are widely studied as an alternative to liposomes because they can be prepared in the same way as phospholipid vesicles [liposomes], but they generally show higher chemical stability" (p.101, right-102, left, line 1). This reference teaches hexasubstituted cyclophosphazene compounds as niosome-forming substances (see abstract, lines 1-3). Although these compounds are not explicitly disclosed as being non-ionic surfactants, a person of ordinary skill in the art would readily recognize the compounds synthesized in the Baroli reference to be nonionic surfactants. In order to successfully form niosomes, the cyclophosphazene derivatives were combined with cholesterol in the presence of dicetylphosphate (an anionic surfactant) to prevent aggregation and subsequently stirred and sonicated (p. 103, section 3.2). Finally, Baroli et al. teach that, using the cyclophosphazene derivatives as niosome-forming substances, vesicles (i.e. niosomes) which have the ability to entrap both hydrophilic and lipophilic compounds (even those with low encapsulation efficiencies) were formed (p.106, see section 4, paragraph 1).

18. It would have been *prima* facie obvious for one of ordinary skill in the art at the time the invention was made to use the niosomes created by Baroli et al. to encapsulate the cationized metalloporphyrin complexes taught by Fridovich et al. Although the combination of Nishihara and Fridovich teaches the metalloporphyrin complexes in liposomes, Baroli et al. teach that

niosomes may be preferable to liposomes because, while they have similar utilities and can be prepared in a similar fashion, niosomes have been shown to have increased chemical stability in comparison to liposomes. Additionally, Baroli et al. disclose the ability of niosomes to encapsulate both hydrophilic and lipophilic compounds, so one skilled in the art would reasonably expect success in the encapsulation of the metalloporphyrin complexes in niosomes.

Conclusion

19. No claims are allowed

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alicia L. Fierro whose telephone number is (571)270-7683. The examiner can normally be reached on Monday - Thursday 6:00-4:30 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Joseph McKane can be reached on (571)272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

10. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

/Alicia L. Fierro/
Examiner, Art Unit 1626

/REI-TSANG SHIAO /
Primary Examiner, Art Unit 1628